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Review

The anatomical basis for disease localisation in seronegative spondyloarthropathy at entheses and related sites

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ABSTRACT

The 2 major categories of idiopathic inflammatory arthritis are rheumatoid arthritis and the seronegative spondyloarthropathies. Whilst the synovium is the primary site of joint disease in the former, the primary site in the latter is less well defined. However, it has recently been proposed that enthesitis-associated changes in the spondyloarthropathies are primary and that all other joint manifestations are secondary. Nevertheless, some of the sites of disease localisation have not been adequately explained in terms of enthesitis. This article summarises current knowledge of the structure, function, blood supply, innervation, molecular composition and histopathology of the classic enthesis (i.e. the bony attachment of a tendon or ligament) and introduces the concept of 'functional' and articular 'fibrocartilaginous' entheses. The former are regions where tendons or ligaments wrap-around bony pulleys, but are not attached to them, and the latter are synovial joints that are lined by fibrocartilage rather than hyaline cartilage. We describe how these 3 types of entheses relate to other, and how all are prone to pathological changes in spondyloarthropathy. We propose that the inflammatory responses characteristic of spondyloarthropathies are triggered at these seemingly diverse sites, in genetically susceptible individuals, by a combination of anatomical factors which lead to higher levels of tissue microtrauma, and the deposition of microbes.

Key words: Enthesis; fibrocartilage; tendons; ligaments; ankylosing spondylitis.

INTRODUCTION

The spondyloarthropathies (SpA) are a group of related conditions that includes ankylosing spondylitis (AS), reactive arthritis, psoriatic arthritis (PsA), undifferentiated spondyloarthropathy and inflammatory, bowel-disease-associated arthritis. Collectively these arthropathies are characterised by inflammatory arthritis, extra-articular inflammation, preceding bacterial infection, seronegativity for rheumatoid factor and a strong HLA-B27 association (Dougados et al. 1991; Calin & Taurog, 1998). Compared with other inflammatory disorders, patients with spondyloarthropathy have a curious propensity for inflammation at the sites where tendons, ligaments (TL) and joint capsules attach to bone. Such sites are known as *entheses*, and thus the inflammation is called *enthesitis*, and insertional disorders in general are *enthesopathies*. Although enthesitis is clinically well recognised in SpA at regions such as the bony attachments of the Achilles tendon and plantar fascia, until recently it was considered independent of other common disease manifestations such as synovitis and sacroiliitis (an osteitis; Calin & Taurog, 1998). However, McGonagle et al. (1998*a*) have now shown by magnetic resonance imaging (MRI) that enthesitis is common in the synovial joints of SpA patients. Furthermore, it is associated with diffuse osteitis in the immediately adjacent bone, suggesting that enthesitis is the unifying concept for SpA (McGonagle et al. 1998*b*). Thus, after a lapse of 3 decades, attention has once again focused on the central importance of the enthesis in SpA pathogenesis (Ball, 1971).

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However, it must be acknowledged at the outset that many of the manifestations of SpA, including osteitis and the peculiar disease distribution at several non-enthesis sites in both the musculoskeletal and other systems, remain difficult to explain in terms of either enthesitis or synovitis. In particular, the prototypic SpA, ankylosing spondylitis, is certainly not confined to entheses—it also affects synovia and several extraskeletal sites (e.g. eyes, heart and lungs). However, while evidence is lacking for enthesitis in every diseased site in SpA, it is still likely that a deeper understanding of these diseases will come from knowledge of the biology and pathophysiology of the enthesis and related structures. For example, a hypothesis stemming from the enthesitis concept is that ankylosing spondylitis targets the interface between bone and fibrocartilage—the latter being a tissue abundant at many entheses (Maksymowych, 2000). We commence by reviewing the structure and function of TL insertions to bone (i.e. the original or 'classic' concept of an enthesis) and continue by assessing the similarities between them and other skeletal sites widely implicated in SpA. We have attempted to explain the distinctive disease distribution in the context of the pathological changes at these locations.

THE CLASSIC CONCEPT OF TENDON AND LIGAMENT ENTHESES

Two types of entheses can be distinguished by their structure and location. They have recently been called fibrous and fibrocartilaginous (Benjamin & Ralphs, 1995, 1997, 1998, 1999, 2000), but German scientists know them as periosteo-diaphyseal and chondral/-chondro-apophyseal attachments respectively (Biermann, 1957; Knese & Biermann, 1958). In addition, Woo et al. (1988) referred to them as indirect and direct insertions. Fibrocartilaginous entheses are typical of the apophyses and epiphyses of long bones, the short bones in the hands and feet and of several ligaments in the spine. Fibrous entheses are characteristic of TL that attach to the metaphyses and diaphyses of long bones. Thus, the tendon insertion of supraspinatus onto the greater tuberosity of the humerus is fibrocartilaginous, but the attachment of deltoid to the roughened tuberosity on the mid-humeral diaphysis is purely fibrous (Benjamin et al. 1986). Many of the sites of fibrocartilaginous entheses in man that are documented in the literature are summarised in Tables 1 and 2, and from them it is evident that the enthesitis associated with SpA is typically a disease of fibrocartilaginous attachments. Such entheses are more common than fibrous ones because, even in long bones, most TL attach to bone close to a joint—and thus to an epiphysis or apophysis. Clearly, the epiphyseal/apophyseal location of ligaments reflects their basic role of maintaining the congruity of joints and guiding or limiting their movements. Most tendons associated with long bones attach near their ends because this increases the speed of action and range of movement of their muscles—albeit at the expense of some mechanical leverage.

In fibrous entheses, the TL attach to the bone (or often the periosteum during childhood) by dense fibrous connective tissue, but in fibrocartilaginous entheses, fibrocartilage cells and matrix are present at the attachment site (Fig. 1 *a*, *b*). It is thus characteristic of such entheses that 4 zones of tissue are recognisable: (1) dense fibrous connective tissue, similar to that typical of mid tendon or ligament; (2) uncalcified fibrocartilage; (3) calcified fibrocartilage; and (4) subchondral bone. Zones 2 and 3 are separated by a calcification front known as the tidemark that typically appears during early adolescence and is comparable to that found in articular cartilage (Havelka & Horn, 1999). It is commonly duplicated, both in TL and in articular cartilage, but it can also be difficult to detect, and its exact functional significance is unclear. What complicates the recognition of zones at a fibrocartilaginous enthesis, is that it is not always simple to classify an enthesis as 'fibrous' or 'fibrocartilaginous': a single enthesis can be both. In most 'fibrocartilaginous' entheses, the fibrocartilage is not uniformly distributed over the entire attachment site. In the appendicular skeleton, it is often more prominent in the deep rather than superficial parts of an insertion site, so that the superficial zone may be more fibrous in character (Benjamin et al. 1986, 1992*a*; Woo et al. 1988; Evans et al. 1990).

The concept of an 'enthesis organ'

Despite the widespread understanding of an enthesis as being the junction between a TL or joint capsule and bone, we now feel that there are compelling arguments for broadening the meaning of the term beyond the confines of its historical origins. Entheses can have a more complex anatomy than can be inferred from focussing exclusively on the TL-bone junction itself, for there can be adjacent tissue specialisations in both the TL and the bone that are functionally related. Indeed, we propose the concept of an 'enthesis organ'. The idea is best illustrated by the Achilles tendon, which Canoso (1998) has elo-

Table 1. *Distribution of fibrocartilaginous entheses in the human upper limb*

Upper limb	Reference
Tendons	
Supraspinatus insertion	Codman, 1934; Benjamin et al. 1986; Kumagai et al. 1994*a*
Infraspinatus insertion	Benjamin et al. 1986
Teres minor insertion	Benjamin et al. 1986
Subscapularis insertion	Benjamin et al. 1986
Pectoralis major insertion	Benjamin et al. 1986
Brachioradialis insertion	Benjamin et al. 1986
Triceps insertion	Knese & Biermann, 1958; Benjamin et al. 1986, 1992*a*
Triceps origin (long head)	Benjamin et al. 1986
Brachialis insertion	Schneider, 1956; Benjamin et al. 1986, 1992*a*
Biceps brachii origin (supraglenoid tubercle)	Knese & Biermann, 1958, Benjamin et al. 1986
Biceps brachii insertion	Schneider, 1956; Knese & Biermann, 1958; Benjamin et al. 1986, 1992*a*; Koch & Tillmann, 1995
Extensor carpi radialis longus insertion	Benjamin et al. 1986
Flexor carpi ulnaris insertion	Benjamin et al. 1986
Abductor pollicis brevis insertion	Benjamin et al. 1986
Tendons arising from common extensor origin	Benjamin et al. 1986; Ipolito, 1986
Tendons arising from common flexor origin	Benjamin et al. 1986
Extensor digitorum communis insertion	Benjamin et al. 1993, Lewis et al. 1998
Ligaments	
Coraco-acromial (acromial end)	Ogata & Uhthoff, 1990
Annular	Benjamin et al. 1986
Radial and ulnar collateral ligaments of the proximal interphalangeal joints	Lewis et al. 1998

The list of sites is not exhaustive, and several others referred to in the early German literature are cited by Beresford (1981).

quently referred to as the 'premiere enthesis' and which he regards as being the enthesis most likely to repay the rheumatologist's attention. The components of the Achilles enthesis organ are the enthesis, sesamoid and periosteal fibrocartilages, the retrocalcaneal bursa and a synovial-covered fat pad (Rufai et al. 1995*a*). Their positional relationships are shown in Figure 2. The sesamoid and periosteal fibrocartilages replace the synovial lining of the bursa in its most distal parts and protect both the tendon and the bone from compression when the foot is dorsiflexed. The bursa promotes a frictionless change in insertional angle according to foot position and the fat pad may be a variable space filler—a plunger that can be protruded or retracted from the retrocalcaneal bursa (Canoso, 1998). The sesamoid fibrocartilage may also dissipate stress at the TL-junction. Indeed in the anterior talofibular ligament of the ankle joint, the presence of a sesamoid fibrocartilage at the talar enthesis, may partly account for the greater frequency of avulsion injuries at the fibular end (Kumai & Benjamin, 2000). Where other tendons or ligaments replace a joint capsule around a synovial joint, articular hyaline cartilage is present instead of a periosteal fibrocartilage and the joint cavity becomes the equivalent of the bursa. The digital extensor tendons of the interphalangeal joints of the fingers and toes provide the best example of this sort of enthesis organ (Fig. 3, Benjamin et al. 1993; Lewis et al. 1998; Milz et al. 1998). They have a prominent sesamoid fibrocartilage, analogous to that in the Achilles tendon and a fatty, synovial fold that protrudes into the joint cavity.

The anatomical concept of a broad view of entheses is of direct pathophysiological relevance, as enthesitis in SpA is associated with diffuse pathological changes in the connective tissues and bone in the immediate vicinity of the insertion (McGonagle et al. 1999*a*, *b*). Periostitis is a well recognised radiographic feature of SpA that should be viewed not only in the context of an 'enthesis organ' (where periosteal fibrocartilage is an important part of the attachment-site complex), but also in the knowledge that periostea elsewhere have much in common with TL entheses (see review by Beresford, 1981). As Beresford notes, periostea-like TL entheses, have the clear potential to become fibrocartilaginous in response to compression and/or shear, serve as sites of bone growth and perhaps most significantly act as sites of entheses for the fleshy, rather than tendinous, fibres of muscles. This reinforces the message of Biermann (1957) that periostea can be insertional structures and that it is

Table 2. *Distribution of fibrocartilaginous entheses in the human lower limb and spine*

Lower limb	Reference
Tendons	
Iliopsoas insertion	Schneider, 1956; Knese & Biermann, 1958; Benjamin et al. 1986
Gluteus medius insertion	Schneider, 1956
Rectus femoris (origin from anterior inferior iliac spine)	Knese & Biermann, 1958
Gastrocnemius (origin of medial & lateral heads)	Benjamin et al. 1986
Semimembranosus insertion	Benjamin et al. 1986
Quadriceps femoris insertion	Evans et al. 1990
Adductor longus (origin)	Ippolito & Postacchini, 1981
Biceps femoris origin (ischial)	Knese & Biermann, 1958
Patellar tendon origin	Evans et al. 1990
Patellar tendon insertion	Evans et al. 1990
Achilles tendon insertion	Schneider 1956; Rufai et al. 1995*a*
Popliteus insertion	Benjamin et al. 1986
Tibialis posterior insertion	Frowen & Benjamin, 1995
Tibialis anterior insertion	Frowen & Benjamin, 1995
Extensor digitorum longus insertion	Milz et al. 1998
Extensor hallucis longus	Milz et al. 1998
Peroneus longus insertion	Frowen & Benjamin, 1995
Peroneus brevis insertion	Frowen & Benjamin, 1995
Ligaments	
Anterior cruciate	Knese & Biermann, 1958; Petersen & Tillmann, 1999*a*;
Posterior cruciate	Petersen & Tillmann 1999*a*
Medial and/or lateral knee menisci	Petersen & Tillmann, 1995
Anterior talofibular (talar and fibular ends)	Kumai & Benjamin, 2000
Sacrotuberous (ischial end)	Knese & Biermann, 1958
Iliofemoral (iliac end)	Knese & Biermann, 1958
Spine	
Annuli fibrosi	François, 1975
Lumbar interspinous and supraspinous	Scapinelli, 1989
Lumbar ligamenta flava	Nakamura et al. 1990; Yoshida et al. 1992

The list of sites is not exhaustive and several others referred to in the early German literature are cited by Beresford (1981).

sometimes difficult in histological sections to distinguish between them and TL entheses. Periostea can even form benign cartilaginous tumours (Molto et al. 2000). However, in the context of SpA, the possibility should also be considered that periostitis is a secondary response to the underlying osteitis that occurs in SpA, for this is the case in neoplasms and infections.

The role and significance of entheses

(1) *Anchorage of soft tissues to bone*. Fundamentally, an enthesis serves to attach TL to bone. At the macroscopic level, a firm union is commonly promoted by the splaying out of TL fibres to create a larger surface area for the enthesis than is present at midsubstance level. In the knee for example, the tibial and femoral insertion sites of the posterior and anterior cruciate ligaments have surface areas that are 3 and 3.5 times that of the ligament substance respectively (Harner et al. 1999). In these and other fibrocartilaginous entheses, the critical site of anchorage at the microscopic level is the calcified fibrocartilage/subchondral bone (CFB) interface (Fig. 1) and not the tidemark: which, as explained above, is just within the TL itself and *not* at the TL/bone interface.

Of key significance therefore is that in both TL and in articular cartilage, the CFB interface is often very complex, with numerous regions of overlap between the interfacing tissues (S. Milz and M. Benjamin, unpublished observations on the Achilles tendon). The overlap regions probably have a major role in strengthening the union of the soft tissues to the bone. Indeed one can imagine that the 'jigsaw' created by the interlocking of the 2 tissues may be so complex that there is little need for direct continuity of collagen fibres across the interface. This is supported by Clark & Stechschulte's (1998) study of the attachment of the quadriceps tendon to the patella. These authors concluded that tendon collagen fibres did not merge with the collagen of bone lamellae, but that they either

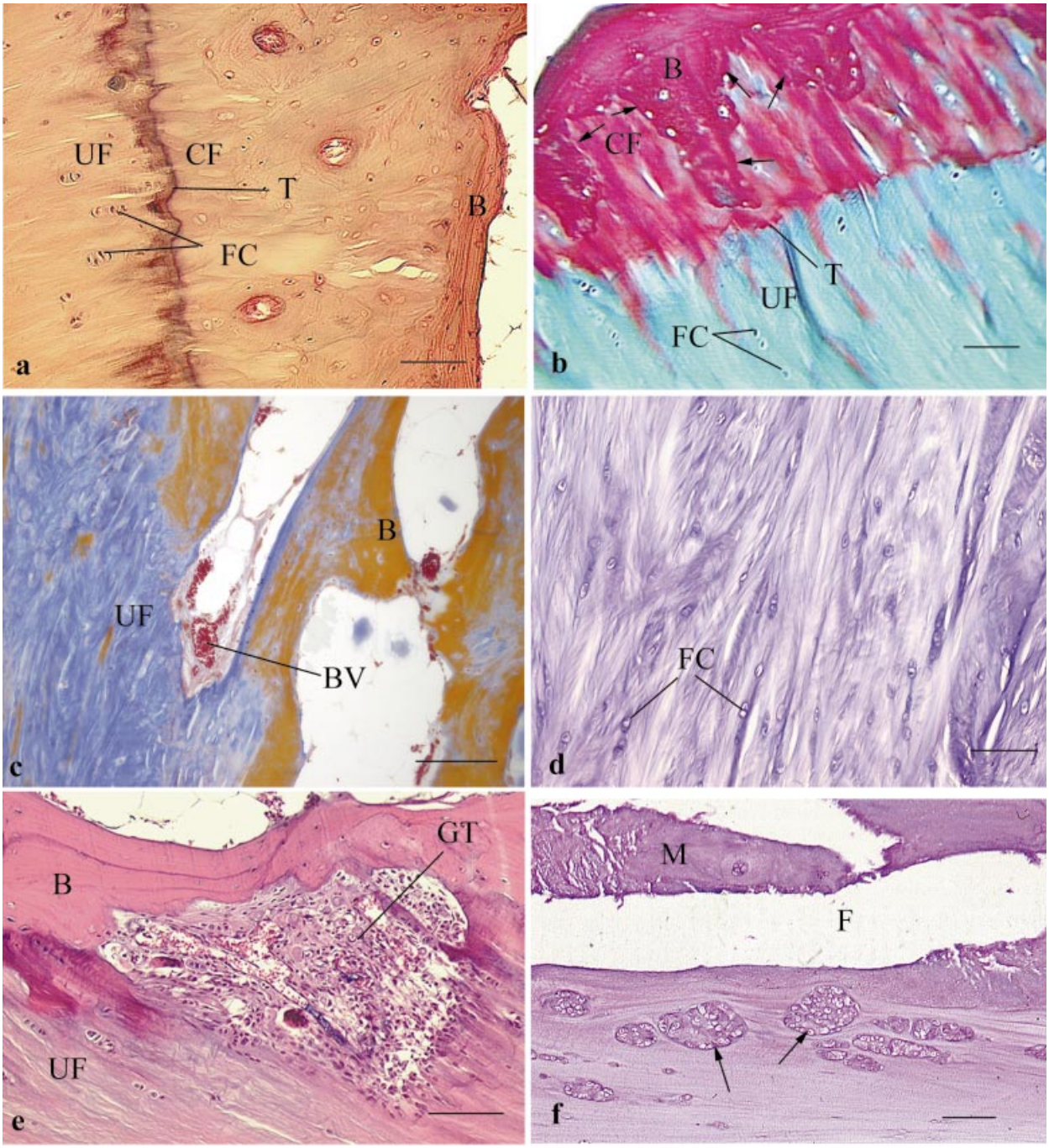

Fig. 1. Histology of entheses and functional entheses. (*a*, *b*) The normal structure of the classic fibrocartilaginous enthesis of the Achilles tendon in sections stained with haematoxylin & eosin (a) and Masson's trichrome. (*b*) The basophilic tidemark separates zones of calcified and uncalcified fibrocartilage and deep to both of these is a remarkably thin layer of subchondral bone. Note that the interface between the calcified fibrocartilage and the bone is highly irregular (arrows in *b*) and that this contrasts strongly with the straightness of the tidemark. (*c*) Blood vessels in the subchondral bone marrow can often make local contact with the uncalcified fibrocartilage at an enthesis. B, bone beneath the attachment of the Achilles tendon in a section stained with Azan. (*d*) Fibrocartilage at the functional enthesis of the tendon of fibularis (peroneus) longus in the region where the tendon grooves the cuboid. Note the fibrocartilage cells lying within a highly metachromatic ECM (the section is stained with toluidine blue) in which bundles of collagen fibres are interwoven are various angles, rather than all being parallel to each other. (*e*) Granulation tissue at the classic enthesis of the supraspinatus tendon. The section is stained with haematoxylin & eosin. (*f*) A longitudinal fissure in the Achilles tendon containing amorphous, metachromatic repair material and associated with several, large, cartilage-cell clusters (arrows). The section is stained with toluidine blue. B, bone; BV, blood vessels; CF, calcified fibrocartilage; F, fissure; FC, fibrocartilage cells; GT, granulation tissue; M, metachromatic repair material; T, tidemark; UF, uncalcified fibrocartilage. Bars, 100 μm.

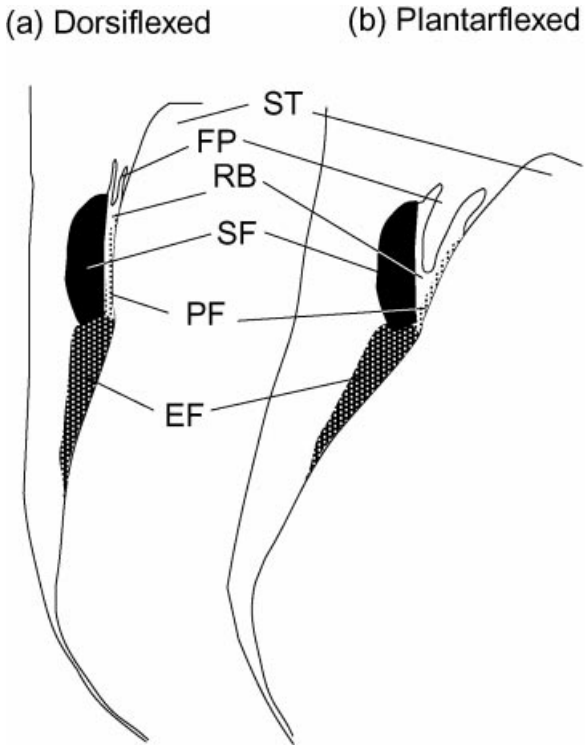

Fig. 2. A diagrammatic representation of the 'enthesis organ' at the insertion of the Achilles tendon in (*a*) a dorsiflexed and (*b*) a plantarflexed foot. The drawings depict midsagittal sections though the Achilles tendon. The enthesis organ comprises an enthesis fibrocartilage that lies at the proximal part of the tendon-bone junction itself, a sesamoid fibrocartilage in the deep part of the tendon, a periosteal fibrocartilage on the superior tuberosity of the calcaneus, a retrocalcaneal bursa between the tendon and bone and a synovial fold associated with the retromalleolar fat pad. They all serve to protect the tendon and/or the bone during dorsiflexion of the foot. EF, enthesis fibrocartilage; FP, fat pad; PF, periosteal fibrocartilage; RB, retrocalcaneal bursa; SF, sesamoid fibrocartilage; ST, superior tuberosity.

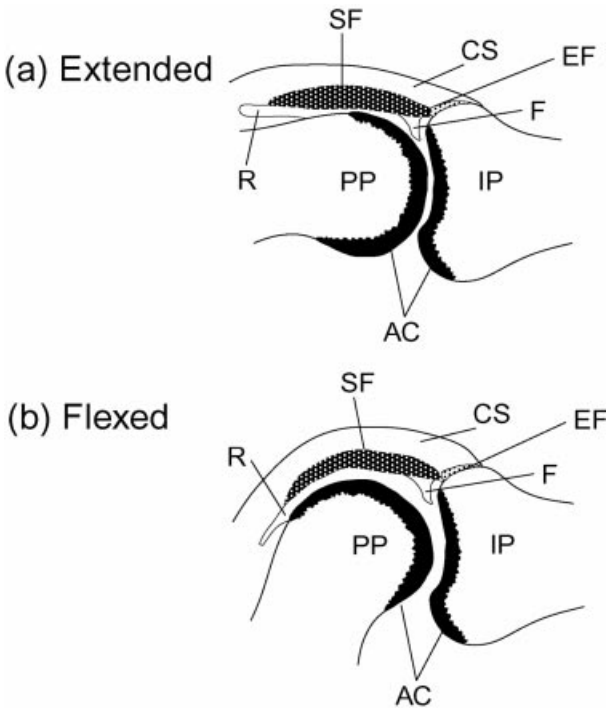

Fig. 3. A drawing of the 'enthesis organ' of the central slip of the extensor tendon in (*a*) an extended and (*b*) a flexed proximal interphalangeal joint. The organ comprises the enthesis fibrocartilage at the attachment of the tendon to the base of the intermediate phalanx, the sesamoid fibrocartilage in the deep part of the tendon, the synovial recess of the joint cavity and the synovial fold that protrudes into the cavity from the central slip. Note that the sesamoid fibrocartilage articulates with the head of the proximal phalanx when the joint is flexed. AC, articular cartilage; CS, central slip; EF, enthesis fibrocartilage; F, synovial fold; IP, intermediate phalanx; PP, proximal phalanx; R, synovial recess; SF, sesamoid fibrocartilage.

ended abruptly at the CFB interface or interdigitated as extensions of calcified fibrocartilage between groups of bone lamellae. Developmental arguments outlined in a later section of this review, make it unlikely that collagen fibres penetrate the bone at fibrocartilaginous entheses; 'true' Sharpey's fibres as such are only characteristic of fibrous entheses. However, all this does depend on what is actually viewed as 'bone' at an enthesis, and it should be noted that Haines & Mohuideen (1968) have called calcified enthesis fibrocartilage 'metaplastic bone' partly because of its permanency in the macerated skeleton. Beresford (1981) has also presented a case for calling such calcified fibrocartilage 'type II chondroid bone'. What may be compared to the classic Sharpey's fibres that characterise fibrous entheses, therefore, are the parallel non-crimped collagen fibres that extend across the tidemark through the zone of calcified fibrocartilage. Nevertheless, the position may be fundamentally different in new entheses created at surgery by anchoring a TL to bone. During the healing of such TL-bone interfaces, several authors have commented on the continuity of collagen across the boundary, which seems to be established early on, and prior to the formation of a definitive fibrocartilage (Liu et al. 1997; Pinczewski et al. 1997). The type III collagen fibres that Liu et al. (1997) describe would seem to be critical in maintaining the integrity of the union.

(2) *Stress dissipation*. The idea that the interlocking of TL and bone at the CFB interface is critical to holding the two tissues together, extends the proposal of Schneider (1956) that enthesis fibrocartilage provides a 2-tier protection mechanism for reducing stress at the bony interface. Schneider (1956) considered that the interlocking guards an enthesis against shear, while the uncalcified fibrocartilage dissipates bending forces during insertional angle changes (i.e. it acts rather like a grommet on an electrical lead). Inoue et al. (1998*a*) have added the useful comment that the role of the calcified fibrocartilage contrasts with that

of the uncalcified tissue in serving to sustain tensile loads under minimal movement.

The underlying assumption behind the suggestion that uncalcified fibrocartilage dissipates bending away from the hard tissue interface is that the ECM stiffens the soft tissue side of the enthesis and enhances its ability to resist compression. The recent reports of aggrecan in enthesis fibrocartilage (Waggett et al. 1998; Milz et al. 1999*b*) support this contention. Aggrecan is the large aggregating proteoglycan typical of articular cartilage, that imparts pressure tolerance on that tissue by virtue of its ability to attract water by capillarity (Heinegård & Oldberg, 1993). Schneider's (1956) ideas on the role of uncalcified fibrocartilage are supported by studies showing a correlation between the thickness of this zone and the degree of insertional angle change that occurs with joint movement (Evans et al. 1990; Benjamin et al. 1991, 1992*a*). If one of the fundamental roles of enthesis fibrocartilage is to dissipate bending away from the bone, this makes the distribution of enthesis fibrocartilage in TL understandable on a mechanical basis: insertional angle changes are always greater at the epiphyses than the diaphyses of long bones (Benjamin et al. 1986; Benjamin & Ralphs, 1998). This suggests that enthesis fibrocartilage is a dynamic tissue that responds to mechanical load and raises the possibility that the quantity of fibrocartilage could vary according to activity levels (see also below). Intriguingly, the quantity of uncalcified fibrocartilage is increased in the patellar tendon of patients with jumper's knee (Ferreti et al. 1983), the ligamenta flava of patients with lumbar spine instability (Nakamura et al. 1990) and reduced in the digital extensor tendons of patients with rheumatoid arthritis (Benjamin et al. 1993).

A further stress-dissipation role is suggested for uncalcified enthesis fibrocartilage by the ability of TL to stretch and recoil, as they do when acting as 'springs' economising on muscular effort during locomotion. When a TL is stretched, it inevitably narrows, and Knese & Biermann (1958) have thus proposed that enthesis fibrocartilage can act as a 'stretching brake' which prevents such narrowing from occurring abruptly at the hard tissue interface. The narrowing is thus displaced more gradually into the TL itself and away from the region of stress concentration at the enthesis.

(3) *Promoting bone growth*. The presence of enthesis fibrocartilage next to the bone opens the possibility for endochondral ossification to occur at the insertion site, as bone grows into the ends of the TL during childhood and adolescence (Knese & Biermann, 1958). This hypothesis is supported by the developmental studies of Gao et al. (1996*a*) on the medial collateral ligament of the rat knee joint. During the growing period, bone grows into the ligament by endochondral ossification, where bone replaces fibrocartilage rather than hyaline cartilage. As at an epiphyseal growth plate, cartilage erosion must be preceded by vascular invasion. Continued bone growth at the enthesis is maintained by the metaplastic formation of new fibrocartilage from the adjacent purely fibrous part of the ligament. Supporting evidence for the metaplastic origin of fibrocartilage cells in ligaments comes from the observations of Hoshi et al. (1997) that local BMP-2 implants induced a similar 'fibroblast-to-fibrocartilage-cell' metaplasia in the ligamenta flava of mice during bony spur formation. Here too, ossification is accompanied by vascular invasion of the newly formed cartilage.

Blood supply of entheses

Enthesis fibrocartilage is avascular (Dörfl, 1969*a*; Benjamin et al. 1986; Petersen & Tillmann, 1995) in line with the general characteristics of fibrocartilage at other sites in the body: notably intervertebral discs. The avascularity explains the distinctive osteological appearance of the sites of fibrocartilaginous entheses: they are smooth, well circumscribed and devoid of vascular foramina (Benjamin et al. 1986). This in turn reflects the lack of any direct communication between blood vessels in the bone marrow and TL at the site of a healthy fibrocartilage enthesis (Scapinelli, 1997). Thus, for infection to spread from bone marrow into a TL, either the fibrocartilage must be degraded or the infection must occur at a fibrous part of the enthesis, where blood vessels could pass between the TL and the bone (Dörfl, 1969*b*).

The lack of blood vessels reflects the compressive forces to which fibrocartilage is subject: vessel lumina would be occluded by compression. However, intratendinous vessels can anastomose directly with those of the bone at fibrous entheses (Dörfl, 1969*b*). It is important to appreciate therefore, that because virtually all so-called 'fibrocartilaginous' entheses are purely fibrous in at least some small part of the attachment site (see above), vascular communication between marrow and TL may still exist at some parts of the insertion site. This point has not been properly addressed in the literature.

Histological observations suggest that vessels in the subchondral bone can penetrate the zone of calcified fibrocartilage and thus reach the tidemark (Schneider, 1956). This also happens in articular cartilage (Meachim & Allibone, 1984). Furthermore, the whole

subchondral plate (i.e. calcified fibrocartilage and bone) can be locally absent at numerous entheses, so that blood vessels in the bone marrow do have restricted local contact with the zone of uncalcified fibrocartilage (Fig. 1*c*). Whether this is a pathological change is unclear, because it could also represent a normal adaptation to improving nutrient access to fibrocartilage cells. This suggestion has been made previously in relation to articular cartilage on the femoral head by Meachim & Allibone (1984). Although Shaibani et al.'s (1993) macroscopic observations on skeletal remains contradict the above assertion, there is nevertheless a suggestion from their work that such enthesial discontinuities are more common in SpA. It seems likely that the osteitis associated with SpA will lead to a secondary destruction of the subchondral plate.

Bizarrely, vascular invasion of enthesis fibrocartilage occurs as part of normal development as the bone grows into the TL at the insertion site (see 'the role and significance of entheses' above). The degeneration of rows of fibrocartilage cells (presumably by apoptosis, by analogy with cell death in the columns of chondrocytes in an epiphysial growth plate) creates small tunnels at the enthesis that are invaded by marrow capillaries and mesenchymal progenitor cells (Gao et al. 1996). The avascular zone is maintained by metaplasia of TL fibroblasts in the pure fibrous zone of the enthesis. What has yet to be addressed is how the blood vessels in the fibrous zone regress as the fibrous tissue is replaced by fibrocartilage.

Nerve supply of entheses

The enthesis is one of the most richly innervated regions of a TL and is particularly well endowed with C and A delta pain fibres (Palesy, 1997). Although encapsulated nerve endings such as Pacinian and Ruffini corpuscles are present in other regions of TL, it is the naked nerve terminals that predominate at entheses (Canoso, 1981). Substance-P immunoreactive nerve fibres have also been located at the entheses of rat coccygeal vertebrae (Imai et al. 1994) and all of these various small diameter, myelinated and non-myelinated fibres could thus be a significant source of entheseal pain, including much spinal pain of unknown aetiology. In this context, Palesy (1997) has presented a useful account of how an exaggerated response to injury occurring at an enthesis could trigger a cascade of events. He presents a scenario in which an injury at an enthesis could trigger a vicious cycle that culminates in chronic muscular pain, even though the original injury may be minor and easily overlooked. This is in line with a similar earlier suggestion of Niepel & Sit'aj (1979) that enthesopathies cannot be regarded as local disorders, but ones that affect the entire locomotor system. It is pertinent, therefore, to note that Nirschl's (1995) recommendations for treating tennis elbow include a regime of strengthening exercises for the entire upper limb and the back. The significant message that emerges from all this, is that a great deal of musculoskeletal pain associated with SpA and rheumatic conditions in general, may start with a problem at an enthesis.

Immunohistochemistry and biochemistry of entheses

Entheses are difficult to study, for they are generally too small to be sampled easily, and the lack of any sharp boundary between pure fibrous tissue and uncalcified fibrocartilage can lead to uncertainty about the exact nature of the tissue studied. There are few entheses suitable for biochemical study and thus most of the information on their molecular composition has come from immunohistochemical studies. However, Niyibizi et al. (1996) and Sagarriga Visconti et al. (1996) have confirmed the fibrocartilaginous character of the interface by identifying types I, II, V, IX and X collagens in pepsin digests and/or immunoblots at the femoral insertion sites of the medial collateral and anterior cruciate ligaments of the steer.

The most comprehensive biochemical/molecular biological study on human material is that of Waggett et al. (1998) on the Achilles tendon. These authors took advantage of the large size of this tendon to conduct a molecular biological and biochemical investigation of the ECM on one sagittal half of the tendon, and to correlate the data with an immunohistochemical analysis conducted on the other half. They sought to compare the fibrous mid tendon with the sesamoid and uncalcified enthesis fibrocartilages. Thus on one half of the tendon, RT-PCR analyses were performed on RNA extracted from the 3 regions, together with Western blots, while the other half of the tendon was sectioned for immunohistochemistry and immunolabelled with antibodies directed against a wide variety of ECM molecules. All regions contained collagen types I, III, V and VI, decorin, biglycan, fibromodulin and lumican, but type II collagen and its mRNA were generally restricted to the fibrocartilages. The distribution pattern of versican and aggrecan mRNA was complementary; the former was restricted to mid-tendon and the latter to the fibrocartilages. Aggrecan distribution is in line

with the general view that this is the large proteoglycan characteristic of cartilage. However, the absence of versican mRNA from the enthesis and sesamoid fibrocartilages, does not fit with the findings of Bode-Lesniewska et al. (1996), who reported versican in both fibro- and elastic cartilages.

There are now a considerable number of immunohistochemical studies on a range of different entheses and the results are summarised in Table 3. Aggrecan and type II collagen have been found in all fibrocartilaginous insertions so far examined and are thus likely to be the best marker molecules for enthesis fibrocartilage. However, the presence of type XI collagen at the entheses of bovine medial collateral and anterior cruciate ligaments (Sagarriga Visconti et al. 1996) may also be highly significant in view of recent evidence suggesting that ossification of the posterior longitudinal ligament of the spine is associated with the candidate gene collagen 11A2 (Koga et al. 1998). It is significant that such ossification starts at the enthesis (Hoshi et al. 1997). Whether type XI collagen is found at other entheses vulnerable to bony spur formation is unknown, but potentially significant if relatively minor ECM proteins are indeed among the early targets for a cellular response to mechanical stress (Chiquet, 1999).

It is curious that type X collagen has been reported by several authors in the zone of calcified enthesis fibrocartilage (Fujioka et al. 1997; Fukuta et al. 1998; Gao, 2000) and this clearly suggests that type X collagen is not a unique characteristic of the hypertrophied chondrocytes of epiphysial growth plates. This is further supported by its presence in the nucleus pulposus and cartilage end plates of intervertebral discs (Roberts et al. 1998). However, the functional significance of this molecule at entheses is unclear, and the only suggestions yet made are purely speculative; there is little or no experimental evidence to support or refute them. Niyibizi et al. (1996) have suggested that type X collagen plays a role in ligament attachment to bone and in maintaining the mineralised status of calcified fibrocartilage, while Gao & Messner (1996) has proposed that it could ensure that the mechanical stiffness of calcified fibrocartilage is intermediate between that of uncalcified fibrocartilage and bone. The underlying presumption, however, that the 4 zones of a fibrocartilaginous enthesis create a gradual change in mechanical properties between TL and bone (Woo et al. 1988) is challenged by the backscattered electron image analysis studies of Boyde et al. (1995) and Vajda & Bloebaum (1999). Their studies of the iliac crest and femur, respectively, strongly suggest that calcified fibrocartilage at TL attachments can have a much higher mineral density than bone.

Intriguingly, Järvinen et al. (1999) have described changes in tenascin C labelling at the rat quadriceps tendon enthesis in animals whose limbs have been cast-immobilised for 3 wk. As the patella is a non-weight bearing bone, the authors suggest that the disappearance of normal tenascin-C labelling at the bony interface that accompanies immobilisation means that expression of the molecule is modulated by mechanical loading. This is in line with the observation that tenascin C is upregulated in fibroblasts grown on attached (i.e. stretched) collagen matrices compared with similar cells grown on a floating (and thus 'relaxed') collagen matrix (Chiquet, 1999). Information is now emerging to show that mechanical stimuli regulate tenascin C transcription, for it is known that its gene promoter contains a 'stretch-responsive' enhancer region (Chiquet, 1999).

Enthesis histopathology

(1) *Microtrauma and inflammation*. Despite the buffering effects of fibrocartilage in dissipating stress at many entheses, an anticipated consequence of wear and tear related to the anchoring properties of the normal enthesis is tissue microtrauma with associated repair. A focus of microtrauma accumulation at entheses could be predicted from estimates of insertion-site deformation that occurs during tensile loading of TL. These have been summarised in an earlier review by Woo et al. (1988) who commented that estimates of strain at insertion sites can be up to 4 times those thought to occur in TL midsubstance. Such data suggest that tissue deformation is marked at the enthesis itself—and if entheses deform when loaded, they must be vulnerable to damage.

When high tensile loads were applied to various entheses from the rabbit knee joint, tendon avulsions occurred at several different levels: the subchondral plate, the interface between calcified fibrocartilage and bone, and the zones of calcified and uncalcified fibrocartilage (Gao et al. 1996*b*). Curiously, avulsions did not occur at the tidemark—the region where there is the most abrupt change in mechanical properties. They were commonest in the subchondral plate, though other workers more frequently report them below this level, i.e. well within the bone itself (see Woo et al. 1988 for a review). This suggests that microfractures are also likely to occur at and below entheses in a variety of overuse injuries and could explain why enthesitis is associated with diffuse underlying osteitis (McGonagle et al. 1998*a*).

Table 3. *ECM macromolecules that have been documented at entheses in man*

ECM molecule	Tendon or ligament (reference)
Type I collagen	Supraspinatus, infraspinatus & subscapularis (Kumagai et al. 1994*a*) Central slip of the extensor tendon in PIP joint (Lewis et al. 1998) Achilles tendon (Waggett et al. 1998) Extensor digitorum longus, extensor hallucis longus (Milz et al. 1998) Transverse ligament of the atlas (Milz et al. 1999*b*) Hamstring grafts used as ACL replacements (Petersen & Laprell, 2000) Suprascapular ligament (Moriggl et al. 2000) Transverse ligament of the acetabulum (Milz et al. 2000)
Type II collagen	Supraspinatus, infraspinatus & subscapularis tendons (Kumagai et al. 1994*a*) Central slip of the extensor tendon in PIP joint (Lewis et al. 1998) Achilles tendon (Waggett et al. 1998) Extensor digitorum longus, extensor hallucis longus tendons (Milz et al. 1998) Transverse ligament of the atlas (Milz et al. 1999*b*) PCL (Petersen & Tillmann, 1999*b*) Lumbar ligamenta flava (Yoshida et al. 1992) Patellar tendon grafts used as ACL replacements (Petersen & Laprell, 2000) Suprascapular ligament (Moriggl et al. 2000) Transverse ligament of the acetabulum (Milz et al. 2000)
Type III collagen	Supraspinatus, infraspinatus & subscapularis tendons (Kumagai et al. 1994*a*) Central slip of the extensor tendon in PIP joint(Lewis et al. 1998) Achilles tendon (Waggett et al. 1998) Extensor digitorum longus, extensor hallucis longus (Milz et al. 1998) Transverse ligament of the atlas (Milz et al. 1999*b*) Suprascapular ligament (Moriggl et al. 2000) Transverse ligament of the acetabulum (Milz et al. 2000)
Type V collagen	Achilles tendon (Waggett et al. 1998)
Type VI collagen	Supraspinatus, infraspinatus & subscapularis tendons (Kumagai et al. 1994a) Central slip of the extensor tendon in PIP joint (Lewis et al. 1998) Achilles tendon (Waggett et al. 1998) Extensor digitorum longus, extensor hallucis longus tendons (Milz et al. 1998) Transverse ligament of the atlas (Milz et al. 1999b) Suprascapular ligament (Moriggl et al. 2000) Transverse ligament of the acetabulum (Milz et al. 2000)
Chondroitin 4 sulphate	Central slip of the extensor tendon in PIP joint (Lewis et al. 1998) Achilles tendon (Waggett et al. 1998) Extensor digitorum longus, extensor hallucis longus tendons (Milz et al. 1998) Transverse ligament of the atlas (Milz et al. 1999*b*)
Dermatan sulphate	Central slip of the extensor tendon in PIP joint (Lewis et al. 1998) Achilles tendon (Waggett et al. 1998) Extensor digitorum longus, extensor hallucis longus tendons (Milz et al. 1998) Transverse ligament of the atlas (Milz et al. 1999*b*)
Chondroitin 6 sulphate	Central slip of the extensor tendon in PIP joint (Lewis et al. 1998) Achilles tendon (Waggett et al. 1998) Extensor digitorum longus, extensor hallucis longus tendons (Milz et al. 1998) Transverse ligament of the atlas (Milz et al. 1999*b*) Suprascapular ligament (Moriggl et al. 2000) Transverse ligament of the acetabulum (Milz et al. 2000)
Keratan sulphate	Central slip of the extensor tendon in PIP joint (Lewis et al. 1998) Achilles tendon (Waggett et al. 1998) Extensor digitorum longus, extensor hallucis longus tendons (Milz et al. 1998) Transverse ligament of the atlas (Milz et al. 1999*b*)
Aggrecan	Achilles tendon (Waggett et al. 1998) Transverse ligament of the atlas (Milz et al. 1999*b*) Suprascapular ligament (Moriggl et al. 2000) Transverse ligament of the acetabulum (Milz et al. 2000)
Versican	Achilles tendon (Waggett et al. 1998)
Lumican	Achilles tendon (Waggett et al. 1998)
Link protein	Human Achilles tendon (Waggett et al. 1998) Transverse ligament of the atlas (Milz et al. 1999*b*)

Table 3. (*cont.*)

ECM molecule	Tendon or ligament (reference)
	Suprascapular ligament (Moriggl et al. 2000) Transverse ligament of the acetabulum (Milz et al. 2000)
Biglycan	Achilles tendon (Waggett et al. 1998)
Decorin	Achilles tendon (Waggett et al. 1998)
Fibromodulin	Achilles tendon (Waggett et al. 1998)
Interleukin-beta, cathepsin D and MMP-1	Torn supraspinatus tendon (Gotoh et al. 1997)

Reduced loading levels can also profoundly affect entheses. In rat limbs cast-immobilised for 3 wk, the fibrocartilage zones of the rat quadriceps tendon dramatically regress (Järvinen et al. 1999).

Microtrauma is a feature of many enthesopathies in addition to those associated with SpA: e.g. medial and lateral epicondylitis (golfer's and tennis elbow respectively), jumper's knee and Osgood-Schlatter's disease. Yet there has been no single, extensive, systematic study by any one individual or group, that compares the histopathology of entheses at a significant number of different sites in the body. All that can be done is to piece together an account based on the work of a number of authors who may have very different interests, viewpoints or expertise and to add a few observations of our own. Histopathological changes documented at entheses include bony spurs (enthesophytes), fissures and cracks, fatty, hyaline or mucoid degeneration, granulation tissue (Fig. 1*e*), small cysts, intratendinous calcification and an increase in the quantity of enthesis fibrocartilage (Schneider, 1956; Ippolito & Postacchini, 1981; Ippolito, 1986; Shaibani et al. 1993; Kumagai et al. 1994*a*; Rufai et al. 1995*a*; Gotoh et al. 1997; Sano et al. 1999). Gotoh et al. (1997) have suggested that the presence of granulation tissue at torn supraspinatus tendons is causally linked to the production of tendon tears. They suggest that IL-1ß, cathepsin D and matrix metalloproteinase 1 expression in the granulation tissue leads to subchondral bone erosion and is thus significant in causing the tears.

There is clear evidence for many of these changes in the Achilles tendon, a site frequently implicated in SpA. One of the more intriguing is the longitudinal fissures that extend from the zone of uncalcified fibrocartilage into the neighbouring dense fibrous connective tissue (Rufai et al. 1995*a*). A repair response to the formation of these fissures is suggested by the amorphous metachromatic material that lies within them and the fibrocartilage cell clusters that surround them (Fig. 1*f*). The association of fissures with cell clusters parallels the early changes that characterise articular cartilage in osteoarthritis. Perhaps the repair material itself is absent in articular cartilage because here the fissures open into the joint cavity, whereas they are enclosed spaces in the tendon. Similarly striking examples of 'tendon osteoarthritis' have also been seen at the insertion of biceps brachii (Benjamin et al. 1992*a*) and of 'ligament osteoarthritis' in the coracoacromial ligament (Ogata & Uhthoff, 1990).

(2) *Enthesophyte* (*bony spur*) *formation*. The enthesis is a common site of ectopic bone formation: not surprisingly when one recalls that it is the site of normal bone growth during development (see above). Enthesophyte formation is typical not only of SpA, but also of several other conditions, most notably diffuse idiopathic skeletal hyperostosis (DISH). Thus ossification at insertion sites gives rise to bony spurs (enthesophytes) at numerous entheses, particularly those of the Achilles and patellar tendons, plantar aponeurosis, coracoacromial (Ogata & Uhthoff, 1990) and spinal ligaments (Scapinelli, 1989; Okada et al. 1991; Shaibani et al. 1993; Hoshi et al. 1997). Spur formation is known to increase with age (Shaibani et al. 1993) and in the posterior longitudinal ligament of the spine (in Japanese populations in particular) spur formation progresses to complete ossification from one enthesis to another, along adjacent segments of the spine (Koga et al. 1998). It is significant to note that such ossification is also reported to have a MHC class II association in Japanese patients (Sakou et al. 1991; Koga et al. 1998). Ossification at most entheses is commonly endochondral, but is occasionally also reported as intramembranous (e.g. Eulderink et al. 1998). Precise details of the formation of large bony spurs in man are lacking, but it is clear that they are often associated with considerable fibrocartilage cell proliferation (Scapinelli, 1989; Ogata & Uhthoff 1990). Small spurs in the rat Achilles tendon can begin with vascular invasion that extends along columns of enthesis fibrocartilage cells, and does so in the absence of microtears or inflammation (Benjamin et al. 2000). The capillaries invade from the underlying bone

marrow and create tunnels that become filled with bone (Benjamin et al. 2000). These observations may provide clues to the pathogenesis of human DISH, which is generally regarded as non-inflammatory enthesopathy. However, despite this clear demonstration of how non-inflammatory enthesophyte formation can commence in the Achilles tendon, one cannot pinpoint particular anatomical sites where inflammatory enthesophytes are more likely to form than non-inflammatory ones (Shaibani et al. 1993).

There is extensive evidence to suggest that the stimulus for the formation of many bony spurs is mechanical and triggered by interactions between bone morphogenetic proteins, activins and/or transforming growth factor (Hayashi et al. 1997; Hoshi et al. 1997; Yonemori et al. 1997). It is well known that bony spurs are common in athletes and that the various tubercles/tuberosities that characterise many bones, develop in response to muscle pull. Direct confirmation of this comes from the work of Rudnicki et al. (1993) in which mice with impaired muscle development were shown to lack bony tubercles. Tubercles are broadly comparable to bony spurs, for both represent osseous extensions of the bone into the tendon; effectively, spurs like tubercles, are traction apophyses (Scapinelli 1989). Okada et al. (1991) have suggested that mechanical stress leads to hypertrophy of the ligamentum flavum and ultimately ossification. Such hypertrophy is also known to be associated with fibrocartilage proliferation (Scapinelli, 1989; Fukuyama et al. 1995).

Notwithstanding the key role of mechanical stimuli in new bone formation at the enthesis where enthesophyte formation appears to be possible in the absence of microscopic inflammation, a major unresolved issue is whether new bone formation leading to joint ankylosis can occur in the absence of preceeding inflammation in subjects with SpA. Ankylosing spondylitis can present with ankylosis of spine in HLA-B27 positive subjects who do not give a history suggestive of an inflammatory response, but this may reflect mild, subclinical inflammation. We need to know whether preceeding inflammation is a prerequisite for entheseal ossification leading to joint ankylosis.

'FUNCTIONAL' ENTHESES: WRAP-AROUND TENDONS AND LIGAMENTS

We have already seen how local anatomical and mechanical factors are closely related to the presence of fibrocartilage at entheses and have argued that there is more to an enthesis than simply the bony interface itself. One extrapolation from this is that the sesamoid and periosteal fibrocartilages that contribute to the formation of an enthesis organ, can also form in other interface regions between a TL and bone—i.e. regions where the 2 tissues are in contact but not attached. Such areas are referred to here as 'functional' entheses to emphasise certain striking similarities between them and the classic entheses described above (Fig. 4). This concept may be important in view of their involvement in SpA (Myerson et al. 1989). Functional entheses are more commonly known as wrap-around TL, as they occur at sites where TL change their direction by *wrapping* around bony pulleys (Vogel, 1995; Vogel et al. 1999). This is well illustrated by tendons that enter the foot from muscles in the leg by passing around the medial and lateral malleoli: e.g. the peroneal tendons and the tendon of tibialis posterior (Williams et al. 1995). The part of the tendon closest to the bone is fibrocartilaginous (Fig. 1*d*), as is the periosteum covering the bony pulley (Benjamin et al. 1995). Sesamoid fibrocartilage is also present in the tendons of extensor digitorum communis, as they cross the metacarpophalangeal joints (Milz et al. 1999*a*), the tendon of biceps brachii where it presses against the radial tuberosity (Koch & Tillmann, 1995) and in the transverse ligament of the atlas where the ligament wraps around the dens (Milz et al. 1999*b*). As at classic entheses, functional entheses are also sites where TL are subject to compression and/or shear—and thus not surprisingly they commonly have a chondrocytic phenotype and are typically avascular (Kolts et al. 1994; Benjamin et al. 1995; Koch & Tillmann 1995; Petersen & Tillmann, 1999*a*, *b*; Petersen et al. 2000). Mehr et al. (2000) have suggested that tenascin C expression by the fibrocartilage cells helps to maintain their cartilage phenotype by decreasing cell-ECM adhesion so that the cells are less deformed when the ECM is stressed. The extent of fibrocartilage differentiation at functional entheses varies with the distance from the surface of the TL where the compression is exerted. The more chondrocytic cells are located nearer to the source of compression, while the more fibroblastic ones lie further away (Ploetz, 1938; Merrilees & Flint, 1980; Malaviya et al. 2000). As we shall see later, they can be subject to similar pathological change.

According to the finite element analyses of Giori et al. (1993) and Haridas et al. (1998), the distribution of fibrocartilage correlates with areas of high compressive stress in functional entheses. More directly, there is also good experimental evidence to suggest that fibrocartilage in these regions represents an

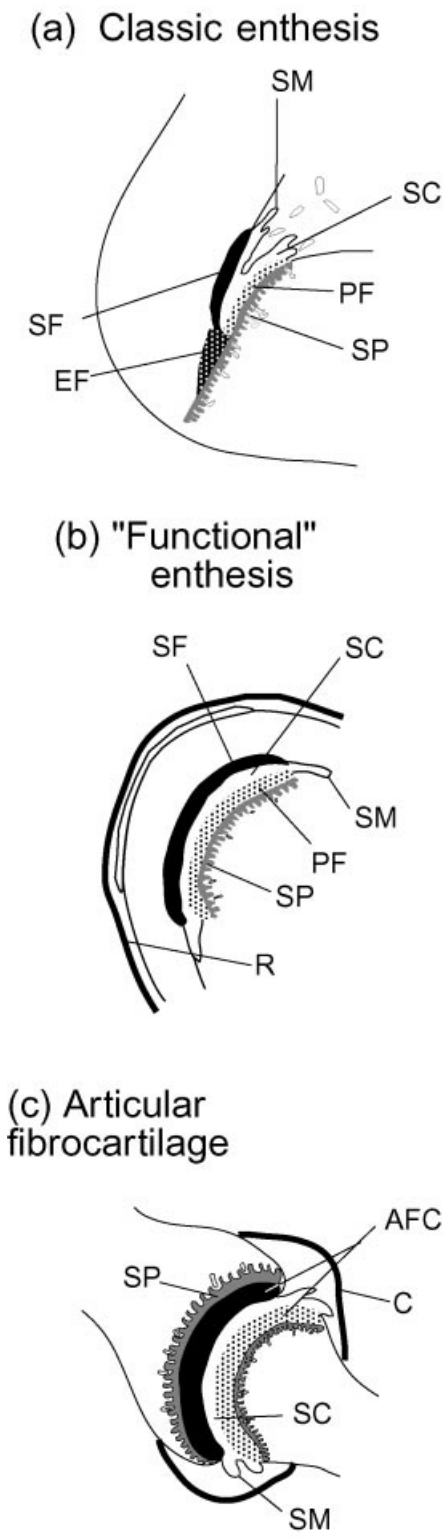

Fig. 4. A diagram to show the similarities between an 'enthesis organ' at a classic enthesis (*a*), functional enthesis (*b*) and an articular fibrocartilage enthesis (*c*). Drawing *a* is based on a sagittal section of an enthesis and drawing *b* shows a longitudinal section of a tendon as it wraps around its pulley. In all cases, there are two opposing regions of avascular fibrocartilage that 'articulate' with each other via a synovial cavity. At least one of the articular cartilages at each site is supported by a thin and vascular subchondral plate. The fibrous retinaculum that holds the 'articulating' tendon and bone together in *b* can be compared both structurally and functionally to the joint capsule that holds the two bones together in *c*. The enthesis fibrocartilage (EF) in *a* has no counterpart at the other two sites. AFC, articular fibrocartilage; C, capsule; EF, enthesis fibrocartilage; P, pulley; PF, periosteal fibrocartilage; R, retinaculum; SC, synovial cavity; SF, sesamoid fibrocartilage; SM, synovial membrane; SP, subchondral plate; T, tendon; TL, tendon or ligament.

adaptation to compression, and that TL are capable of detecting changes in mechanical load and responding appropriately. A number of authors have rerouted tendons surgically so that either a tendon that runs a straight course becomes a wrap-around one, or vice versa (Ploetz, 1938; Gillard et al. 1979; Malaviya et al. 2000). Fibrocartilage formation occurs in a tendon that is translocated around a bony pulley, but regresses where surgery creates a more direct course for the tendon. In tendons that are removed from their bony contact, there is a good correlation between their altered structure and function. The reduction in GAG content correlates well with the reduced thickness of the fibrocartilage region and its affinity for alcian blue. It is also associated with a decreased ability of the fibrocartilage to resist compression as indicated by the increased rate of compressive creep and equilibrium strain in confined compression tests (Malaviya et al. 2000). As Pauwels (1960) has highlighted in his 'causal theory of histogenesis', fibrocartilage formation only occurs on the concave side of the tendon that is made to wrap around a new bony pulley and not on its convex side. This suggests that a combination of compression and shear, but not shear alone provides the mechanical stimulus for fibrocartilage formation. In vitro studies also support the suggestion that fibrocartilage development is a response to compression (Koob et al. 1992). It is also intriguing to note that when the tendon of the long head of biceps is ruptured in vivo, the periosteal fibrocartilage lining the intertubercular sulcus disappears (Benjamin et al. 1992*b*). Thus in the absence of compression and shear, the chondrocytic phenotype is no longer maintained and a loose connective tissue resembling a synovium is present instead.

Where fibrocartilage is formed de novo in TL, either native fibroblasts must undergo metaplasia to become fibrocartilage cells, or mesenchymal stem cells have to migrate into the areas and differentiate along chondrocytic pathways. Although there are progenitor cells in bone marrow capable of differentiating into cartilage, bone or fibrous tissue when implanted in appropriate tissues (Prockop, 1997), it is difficult to envisage how they could form fibrocartilage at functional entheses. There is no direct route from bone marrow to any functional enthesis that is some

distance from the insertion site. It is possible that progenitor cells could migrate from the subchondral bone marrow to form enthesis fibrocartilage, for a comparable stem cell migration occurs during the healing of articular cartilage (Johnstone & Yoo, 1999). However, it seems far more likely that the fibrocartilage cells arise by fibroblastic metaplasia, as both are arranged in similar longitudinal rows.

Tenosynovitis is a feature of SpA, especially in large weight-bearing joints adjacent to the enthesis. It may relate to enthesitis and be a cytokine-mediated, secondary inflammation (McGonagle et al. 1998*b*). However the swelling can also be a considerable way from the insertion site and occur at functional entheses such as those described above. Sites where inflammation is common include the medial and lateral malleoli. From the foregoing discussion we have noted that classic entheses are subject to microtrauma and features compatible with microscopic inflammation. Certainly, evidence of microtrauma similar to that which occurs at the intratendinous, sesamoid fibrocartilages of classic entheses has been documented at some functional entheses in the foot (Benjamin et al. 1995). The changes include fissuring, fragmentation and chondrocyte clustering in the surface fibrocartilage. Functional entheses also appear to be targets for disease in SpA (see fig. 2 in McGonagle & Emery, 2000). We suggest that such similarities in pathology between true and functional entheses may stem from underlying parallels in their anatomy and histology.

'ARTICULAR' FIBROCARTILAGINOUS ENTHESES

Thus far we have seen how fibrocartilage that is associated with resisting compression and/or shear is found at both classic and functional entheses. It is interpreted as an adaptation to resisting compression and/or shear in addition to enabling the tendon to continue transmitting tensile load. Here we draw attention to several synovial joints that are lined by fibrocartilage and which are also known targets in SpA, and present a case for considering them as having 'articular' fibrocartilaginous entheses (Figs 4, 5). We feel that this usefully draws attention to basic similarities between seemingly disparate sites implicated in SpA.

There are striking parallels between the junction of bone with articular cartilage and its junction with TL enthesis fibrocartilage. At both locations, there is a thin subchondral plate with associated bone marrow blood vessels, an irregular interface between calcified (fibro)cartilage and subchondral bone, and one or more tidemarks defining the border between calcified and uncalcified (fibro)cartilage (see e.g. Buckwalter & Hunziker, 1999 for a recent review). Generally, SpA does not affect the subchondral bone in the immediate vicinity of the articular cartilage that lines synovial joints, but where such joints are lined with *fibrocartilage* rather than *hyaline* cartilage, the changes can be pronounced (D. McGonagle, personal observations). This may be of fundamental importance in understanding the pathogenesis of SpA-disease in the sacroiliac, sternoclavicular, acromioclavicular and temporomandibular joints. In all these joints, the presence of fibrocartilage may suggest that the levels of shear are higher than those in joints lined with hyaline cartilage. One could also speculate that in turn the shear forces operate throughout a greater depth of the articular surface and even exert an effect on the underlying bone. As we shall see this may be crucial in subchondral osteitis in sacroiliac joints (Ahlstrom et al. 1990), that resembles peri-entheseal osteitis as seen by MRI.

The sacroiliac joint (*SIJ*)

The human SIJ is an atypical synovial joint with a limited range of movement and unusually rough articular surfaces that are characterised by a series of elevations and depressions (Williams et al. 1995). As sacroiliitis is the earliest feature of AS, this joint could well hold an important key to unravelling the pathogenic mechanisms of the disease. However, virtually all the structures in the SIJ and adjoining tissue may be abnormal in AS and hence the nature of the primary lesion is highly contentious. Although a primary role for enthesitis at this site has not been considered, an immune attack against synovium has been proposed (Braun & Sieper, 1996; François et al. 2000). The pathological changes in the sacroiliac joint are considered here in the context of changes in the bone, as subchondral osteitis is considered the earliest site of sacroiliac disease localisation (Ahlstrom et al. 1990). Curiously, the abnormalities in AS have a predilection for the iliac side of the joint, and inflammation is generally more severe in this region. Other conditions of the ilium (e.g. osteitis condensii iliitis, DeBosset et al. 1978) may relate to weight-bearing during pregnancy and also localise to the iliac side. It is intriguing to note therefore that there are important anatomical differences between the 2 sides of the joint and that the differences also change with age. In the child, the sacral side is lined by hyaline cartilage, and the iliac side by fibrocartilage, but in the adult, and in contrast to the traditional view, large

parts of the iliac articular cartilage also become more hyaline (Kampen & Tillmann, 1998). The changes start around puberty, but exactly when the fibrocartilage disappears completely is not known. Perhaps significantly, it seems that the iliac cartilage undergoes a characteristic sequence of age-related changes resembling those that occur in other joints in osteoarthrosis—notably fibrillation and chondrocyte clustering (Kampen & Tillmann, 1998). Kampen & Tillmann (1998) argue that the changes are a normal component of ageing and occur in the absence of clinical symptoms. Such 'physiological' degeneration is rarely a feature of the sacral side of the joint.

A prominent feature of sacroiliitis is the diffuse osteitis that seems to undermine the articular cartilage. Although the SIJ has extensive areas of strong ligament attachments that could contribute to enthesitis and associated osteitis, the possibility that the articular cartilage contributes to the disease process also needs exploration. As in the enthesis that exists between a TL and bone, the articular fibrocartilage 'enthesis' has a straight tidemark that separates zones of calcified and uncalcified fibrocartilage, and a highly irregular interface between calcified fibrocartilage and bone. Intriguingly, large defects in subchondral bone that have become filled with cartilage can sometimes be observed on the iliac side of the joint (Kampen & Tillmann, 1998). These correspond to the local absence of subchondral bone that can also be seen in tendon entheses (Evans et al. 1990). Like TL entheses, the fibrocartilage/bone enthesis at the SI joint also resists shear, so the 2 types of entheses do share anatomical, histological and biomechanical similarities. Importantly, shear is greater on the iliac side of the joint, for the sacral side is loaded in a more perpendicular fashion (Kampen & Tillmann, 1998), and on MRI the pathological changes are reminiscent of changes adjacent to sites of enthesitis.

A number of suggestions about the involvement of the SIJ in SpA can be made in the light of Kampen & Tillmann's (1998) findings. Firstly, the SIJ changes on MRI are similar to enthesitis in the knee (McGonagle et al. 1998*a*) and indeed similar to functional entheses discussed earlier. These observations suggest this joint behaves like a TL enthesis in SpA. In genetically susceptible individuals, the shear forces acting on the iliac side of the joint may contribute directly to disease localisation at the SIJ in a manner similar to that at other sites. Secondly, the curious tendency of the joint to show 'physiological' wear and tear on its iliac side alone, suggests that microtrauma may play a role in disease localisation. Thirdly, the rarity of onset of AS after the age of 40 years, may be linked to the extensive replacement of fibrocartilage by hyaline cartilage on the iliac side of the joint. Finally, the relative absence of sacroiliitis in children, despite abundant fibrocartilage at the SIJ, may indicate that changing biomechanics with age, together with the ageing changes themselves, could contribute to the emergence of spinal disease in later life.

The temporomandibular joint (TMJ)

The TMJ is occasionally involved in ankylosing spondylitis and reactive and psoriatic arthritis. As with so many other sites implicated in SpA, the TMJ is rich in fibrocartilage. This forms the articular cartilages on both the skull and the mandibular sides of the joint, and is also represented by an articular disc that subdivides the joint cavity into upper and lower parts (Fig. 5). The TMJ is not a typical weight-bearing joint, like the large joints of the knee or hip. The principle loading is shear that arises during the twisting and sliding movements that the fibrocartilage disc and the articular condyle undergo (Moss, 1983). Fibrocartilage is highly characteristic of sites where such forces are substantial (Benjamin & Evans, 1990). Furthermore, the TMJ is notoriously vulnerable to wear and tear, and among the most common histopathological changes is the proliferation of fibrocartilage on the mandibular head and articular eminence (Castelli et al. 1985). At least some signs of degeneration are virtually universal by old age. Finally, a key point about any pathological process affecting the TMJ is that the joints on either side of the body are coupled mechanically. Thus, restricted movement that comes from SpA involvement on one side of the jaw inevitably affects the other, even though the joint on the other side may be quite normal.

Sternoclavicular, acromioclavicular and manubriosternal joints

These joints are implicated in SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis), an unusual syndrome in which certain musculoskeletal disorders are associated with various dermatological conditions. Like the SIJ joint of the young child, the sternoclavicular, acromioclavicular and manubriosternal joints are lined with fibrocartilage and are associated with diffuse osteitis immediately adjacent to the cartilage. Although SAPHO is generally recognised as part of the spectrum of SpA, it is occasionally excluded because of its anatomical distribution and lack of HLA-B27 association. The earliest changes in

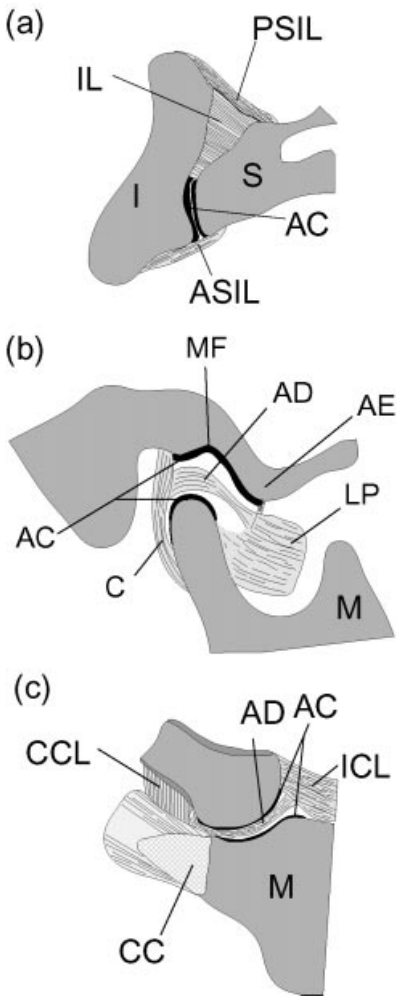

Fig. 5. Three synovial joints with articular fibrocartilage entheses that are commonly implicated in SpA – the sacroiliac joint (*a*; transverse section), the temporomandibular joint (*b*; sagittal section) – and the sternoclavicular joint (*c*; coronal section). In each joint, one or both articular cartilages are fibrocartilaginous. Additionally, a fibrocartilaginous articular disc is present in the temporomandibular and sternoclavicular joints. AC, articular cartilage; AD, articular disc; ASIL, anterior sacroiliac ligament; AE, articular eminence; C, capsule; CC, costal cartilage; CCL, costoclavicular ligament; I, ilium; ICL, interclavicular ligament; IL, interosseous ligament; LP, lateral pterygoid muscle; M, mandible; MF, mandibular fossa; PSIL, posterior sacroiliac ligament; S, sacrum.

SAPHO resemble enthesitis and the MRI appearance is similar (Maugars et al. 1995). The disease most characteristically affects the sternoclavicular joint, but can also occur in the acromioclavicular, manubriosternal joints and temporomandibular joints (Marsot-Dupuch et al. 1999). It is thus intriguing that all 3 joints have fibrocartilage associated with them. The clavicular end of both the sternoclavicular and acromioclavicular joints is covered with fibrocartilage, because the clavicle develops as a membrane bone. Additionally, fibrocartilaginous menisci may partially or completely subdivide both joint cavities into 2 compartments (Fig. 5). The manubriosternal joint is a slightly moveable symphysis between the manubrium and body of the sternum. The ends of the bones are covered with hyaline cartilage, but the bones are united by fibrocartilage. Intriguingly, synostosis commonly occurs between the manubrium and body of the sternum as a consequence of normal ageing, let alone in SpA.

THE REGIONAL BASIS OF DISEASE LOCALISATION IN SKELETAL-ASSOCIATED SITES

Thus far we have focused on the anatomy, physiology and pathology of 'classic' entheses, and introduced the concepts of the 'functional' and 'articular' fibrocartilage entheses. Here, we concentrate on more general aspects of the sites of SpA lesions in the light of the enthesitis-based lesions.

General principles relating to tissue involvement

Bone. Enthesitis is associated with diffuse inflammatory changes in the underlying bone in about 40-50% of patients with SpA (McGonagle et al. 1998*a*). These changes are evident at the plantar fascia and other sites, but their pathogenesis is ill defined (McGonagle et al. 1999*c*). Many of the inflammatory lesions extend into the underlying bone for a considerable distance and in large synovial joints, the bone changes may follow stress lines arising from the enthesis (see fig. 4 in McGonagle et al. 1998*a*). Such stress lines are known to be associated in the patellar tendon enthesis with a distinctive pattern of trabecular orientation that probably determines the capacity of the cancellous bone to transmit load (Inoue et al. 1998*b*). What is the basis for the inflammatory changes in the bone? We have already discussed how the interdigitating attachment of the zone of calcified fibrocartilage to the subchondral bone represents the true interface in the TL-bone connection and not the tidemark per se, and this may partly explain the propensity for associated changes in the underlying bone. Numerous small blood vessels can reside at the interface, nestling in the marrow just below the interdigitations. This network of vessels may have implications for bacterial (or bacterial product) deposition at entheses in patients with SpA (Schultz et al. 1985). It has been argued that the pathological changes in the bone occur adjacent to fibrocartilage, and are therefore secondary to autoimmunity directed against that tissue (Maksymowich, 2000). However, the bone changes may occur at a considerable distance from fibrocartilage, are extensive and sometimes follow the lines of biomechanical joint stressing (see fig. 4 in McGonagle et al. 1998*a*).

Curiously, anchorage of a TL to bone is not necessary for the underlying osseous changes to occur, for functional entheses can behave in the same way. Makysomwych (2000) has recently drawn attention to the presence of SpA-associated osteitis in the region of the cuboid bone where it is grooved by the tendon of peroneus longus. This further supports the concept that structures that share some of the structural and functional features of true entheses are also subject to the same pathological changes.

Synovium. It has been proposed that pathological changes in synovial joints in SpA are secondary to the liberation of pro-inflammatory mediators from the enthesis and adjacent inflamed bone (McGonagle et al. 1998*b*). Without definitive proof, this concept was accepted as the likely mechanism for synovial inflammation in SpA (Sieper et al. 2000). However, based on what we have proposed thus far, this does not mean that immune reactivity within the joint represents a secondary or bystander response. Wherever TL fuse with the capsules of synovial joints, any sesamoid fibrocartilages on their deep surfaces are in direct contact with the joint cavity. This suggests that some of the clonal lymphocyte populations in joints may be directed against entheseal antigens, although the synovitis itself may be secondary. However, a major unresolved issue is that the enthesis fibrocartilage is normally avascular. Consequently, if autoimmunity against fibrocartilage antigens is indeed important in SpA, it must be preceded by pathological changes that expose the fibrocartilage to blood-borne lymphocytes (Makysomwych, 2000).

Specific regional sites

Hand. The small synovial joints of the hands have a characteristic pattern of disease in the various arthropathies. The distal interphalangeal (DIP) joints are well documented sites for osteoarthritis (Heberden's nodes) and recognised target organs in SpA, but not RA. Metacarpophalangeal (MCP) joints are infrequently affected by OA, but almost universally implicated in RA. Psoriatic arthritis, a subset of SpA, is associated with MCP disease, but there is much controversy about whether its reported involvement really represents RA (McGonagle et al. 1999*d*). Finally, the proximal interphalangeal (PIP) joints are affected by all three arthropathies.

As mentioned earlier, the PIP and DIP joints are unusual in having extensive sesamoid fibrocartilages in the extensor tendons that replace the dorsal joint capsule (Fig. 3; Benjamin et al. 1993; Lewis et al. 1998; Milz et al. 1998). These fibrocartilages protect the tendons from compression when the digits are flexed, and provide an articular surface for the head of the phalanx that is just as extensive as that provided by the adjacent bone (Fig. 3). The degree of direct contact between fibrocartilage and joint cavity is even more impressive when one realises that both the collateral and palmar ligaments are also highly fibrocartilaginous (Fig. 6; Lewis et al. 1998). The palmar ligament replaces the capsule on the ventral aspect of the joint, and provides a vital restraint against interphalangeal hyperextension (Benjamin et al. 1993). Thus, when the distribution of the capsular fibrocartilages is viewed in its entirety, the picture that emerges is one of a continuous fibrocartilaginous cup that extends from the base of the more distal phalanx and receives the head of the more proximal one.

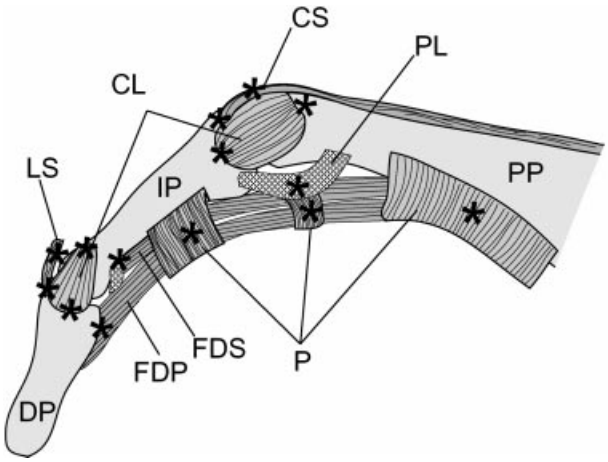

Fig. 6. The numerous sites of fibrocartilage (asterisk) associated with a finger. Fibrocartilage is present in the pulleys that hold the tendons of flexor digitorum superficialis and profundus in place and at the classic entheses associated with the central and lateral slips of the extensor tendon and the collateral ligaments of the interphalangeal joints. Fibrocartilage also comprises the palmar ligaments of the joints and is present as a sesamoid fibrocartilage in the extensor tendon as it passes over the interphalangeal joints. CS central slip, CL collateral ligaments, DP distal phalanx, FDS flexor digitorum superficialis, FDP flexor digitorum profundus, IP intermediate phalanx, LS lateral slip, P pulley, PL palmar ligaments, PP proximal phalanx. (Modified from fig. 105 in Guyot J (1990) *Atlas of Human Limb Joints*, 2nd edn. Berlin: Springer.)

There is much less fibrocartilage in the dorsal aspect of the MCP joints, for here the sesamoid fibrocartilage in the extensor tendon does not contact the joint cavity directly (Milz et al. 1999*a*). It is separated from it by a fibrous capsule and bursal-like, peritendinous loose connective tissue. Furthermore, the extensor tendon does not insert near this joint, so it has no enthesis fibrocartilage at the site. Nevertheless, the palmar ligaments are still prominent fibrocartilages that articulate with the metacarpal heads.

Dactylitis, which affects the small joints of the fingers, is a characteristic feature of SpA but not RA.

The available sonographic and MRI evidence suggests that it is predominantly flexor tenosynovitis without synovial joint synovitis (Olivieri et al. 1996). However, the tenosynovitis is surprising because rheumatoid arthritis (the most common cause of severe synovitis) is not associated with dactylitis. Enthesitis of the flexor tendons and joint capsules has also been suggested as a potential mechanism (McGonagle, 1998*b*), but the diffuse nature of dactylitis has long puzzled rheumatologists. However, an anatomical basis for such changes is easy to imagine, for in addition to the enthesis and sesamoid fibrocartilages described above in association with the extensor mechanism, there are entheses along much of the length of the digits, at the attachment of the fibrous flexor sheaths to the phalangeal shafts. There is a fibrous flexor sheath in each finger that creates an extended, osteofibrous tunnel through which the flexor tendons pass (Fig. 6). The sheath is reinforced at intervals by a series of pulleys which prevent the tendons from bowstringing: and at least some of these are fibrocartilaginous (Sampson et al. 1991; Katzman et al. 1999). Fibrocartilage may also be present in one or both of the flexor tendons at the point where flexor digitorum superficialis (FDS) splits to allow the tendon of flexor digitorum profundus to pass on to the terminal phalanx. The 2 tendons are compressed against each other in this region when FDS contracts. Just as compression between tendon and bone leads to the development of a functional enthesis, so too can compression between 2 tendons induce fibrocartilage formation and possibly leads to similar degeneration.

Foot. The Achilles tendon and plantar fascia are the most commonly implicated sites in SpA-associated enthesitis. Their vulnerability to damage is probably multifactorial, but in the context of the current review, mechanical factors, and the prominence of fibrocartilage at both entheses are regarded as particularly important. The 3 fibrocartilages of the Achilles enthesis organ have been described earlier (see also Fig. 2), and the unpublished observations of T. Kumai & M. Benjamin suggest that the calcaneal plantar fascia enthesis is one of the most fibrocartilaginous in the body. A direct mechanical link between the tendon and fascia is promoted by the direct continuity of some of their fibres over the surface of the calcaneus (Williams et al. 1995). The large size of the Achilles tendon, its site of insertion and the contribution to its formation of 2 large muscles of contrasting organisation are undoubtedly significant in accounting for its vulnerability to damage. Its calcaneal attachment means that the tendon is influenced by movements at both the subtalar and ankle joints, and is thus subject to rotational forces that are distributed non-uniformly across the entire width of its enthesis (Myerson & McGarvey, 1998). This imparts high stresses on the insertion site, especially in subjects who are flat-footed. The wear-and-tear is accentuated by the cam-like action of the superior tuberosity on the tendon, during dorsiflexion of the foot (Rufai et al. 1995*a*). The 2 large muscles that principally contribute to the formation of the Achilles tendon are soleus and gastrocnemius. The former is a fatigue-resistant, postural muscle whose activity ensures that the tendon is loaded for long periods during standing as the leg is balanced on the foot (Myerson et al. 1998). In marked contrast the latter is both a double-headed and a biarticular muscle. It is gastrocnemius that supplies the power for running and jumping and it thus contributes significantly to the extreme loading to which the tendon may be subject (up to 6–8 times body weight, Soma & Mandelbaum, 1994). Biomechanical modelling studies suggest that the plantar fascia can carry 14% of the load on the foot during the stance phase of the gait cycle (Kim & Voloshin, 1995) and its surgical release suggests that it plays an important role in maintaining the medial longitudinal arch of the foot. Complete severance of the fascia significantly collapses the arch and this in turn strains other regions of the foot (Murphy et al. 1998).

Other regions of the foot, including the cuboid, navicular and cuneiform bones, are curiously targeted in the juvenile form of SpA. The changes lead to foot ankylosis and are similar to those affecting the spine in AS patients (Burgos-Vargas & Vazquez-Mellado, 1995). Although tarsal union is not restricted to SpA, it is still typical of young people and is thought to be a developmental anomaly, that is genetically linked and which results from a failure of joint cavitation (Regan et al. 1999). Indeed, the cuboideonavicular joint normally lacks a joint cavity, for it is more commonly a fibrous than a synovial joint (Williams et al. 1995). Tarsal unions can be osseous or non-osseous and affect a number of joints. In a histopathological survey of a large number of non-osseous, talocalcaneal, calcaneonavicular and naviculocuneiform unions, Kumai et al. (1998) found that the bones were almost universally linked by fibrocartilage. Indeed, this is a general feature of pseudoarthroses (Urist et al. 1954; Pritchard, 1963). There was evidence of microtrauma in the fibrocartilage tissue at the site of the union, with considerable vascular proliferation, osteoblastic and osteoclastic activity that is reminiscent of the changes occurring in certain enthesopathies. Thus, Kumai et al. (1998) have compared their histo-

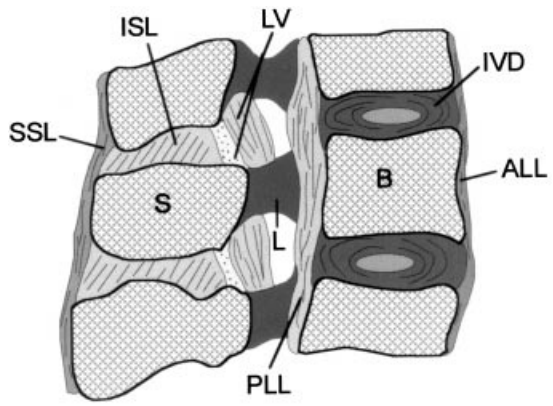

Fig. 7. The profusion of ligaments associated with the spine. The annulus fibrosus of the intervertebral discs, together with the anterior and posterior longitudinal ligaments link adjacent vertebral bodies together, the interspinous and supraspinous ligaments link adjacent spines and the ligamenta flava connect adjacent laminae. Many of the ligaments have fibrocartilaginous entheses. Abbreviations: ALL anterior longitudinal ligament, B vertebral body, IVD intervertebral disc, ISL interspinous ligament, L lamina, LF ligamentum flavum, PPL posterior longitudinal ligament, S spine, SSL supraspinous ligament. (Modified from fig. 4.23A in Williams PL & Warwick R (1980) *Gray's Anatomy*, 36th edn. Edinburgh: Churchill Livingstone.)

pathological findings with those documented at the patellar tendon enthesis in Osgood-Schlatter's disease and the tibialis posterior tendon in accessory navicular enthesitis.

Shoulder and hip. When ankylosing spondylitis involves the upper limb, there is a propensity for shoulder disease, with radiographic evidence for prominent enthesitis. It is well known that the rotator cuff region is a common site of microtrauma, that there is extensive fusion of the rotator cuff tendons with the shoulder joint capsule and that the tendons have prominent enthesis fibrocartilages (Benjamin et al. 1986). Furthermore, the perimeter of the articular cartilage covering the humeral head is fibrocartilaginous where it lies next to the attachments of the rotator cuff. These may all be important factors in explaining why the shoulder joint can be involved in SpA.

Joint failure due to complete capsular ossification in the hip is common in AS. As enthesitis is associated with endochondral ossification extending into TL at different sites, then it is possible that this response is related to enthesitis. However, it seems more likely to be linked to chondroid metaplasia within the capsule itself. This is exceedingly common in other conditions associated with mechanical stress of the hip joint. Thus, it is present in the capsules of patients with dislocated hip arthropathy because of the pressure of the capsule against the articular cartilage of the femoral head (Yutani et al. 1999) and in nearly 50% of osteoarthritic hips (DiFrancesco & Sokoloff, 1995).

Vertebral column. Except for the facet and costovertebral joints, and the specialised joints of the suboccipital region, much of the spine is devoid of synovium. However, a bewildering variety of TL are associated with the spine, and there are a greater number of entheses crowded onto individual vertebrae than onto many bones of much greater size. The anterior and posterior longitudinal ligaments, annuli fibrosi, ligamenta flava and nuchae, interspinous and supraspinous ligaments, the numerous components of the erector spinae and transversospinalis muscle groups are some of the TL competing for limited attachment areas. Generally, much of the available attachment area seems to be devoted to ligaments rather than tendons (Fig. 7) and thus enthesopathy in the spine seems predominantly to be a ligamentous phenomenon.

There is a general consensus that most of the spinal pathological changes in SpA relate to enthesitis and it is thus significant that fibrocartilaginous entheses are prominent in several spinal ligaments (see Table 2) and subject to a great deal of degenerative change, even in non-SpA patients (Scapinelli, 1989). The profusion of fibrocartilaginous entheses in the spine probably reflects the rotatory and compressive forces that act upon it: and rotation means significant shear. Histopathological changes include fibrocartilage cell proliferation and bony spur formation, and are common at the attachments of the lumbar interspinous and supraspinous ligaments (Scapinelli, 1989). The bony spurs could even represent an ageing response that compensates for the progressive stiffness of the spine that is typical of older people, by increasing the lever arm for muscle action (Scapinelli, 1989). In practice, such a mechanical advantage is probably nullified by the narrowing of intervertebral discs that also occurs with age (Scapinelli, 1989). The frequency of degenerative change in spinous ligaments could be linked to the short length, but wide range of movement of ligaments that only span across one segment of the spine.

A characteristic site of disease in RA is the atlantoaxial region, where the synovitis-associated inflammatory process destroys bone and cartilage. As this region is also a target in SpA, it is envisaged that similar inflammatory changes play an essential role in joint destruction. However, 2 major factors associated with disease localisation elsewhere in SpA, namely the presence of fibrocartilage and microtrauma also characterise this site. It is intriguing to note therefore that the mechanical stability of the atlantoaxial complex can be compromised by a gradual degeneration of the transverse ligament (Zeidman & Ducker,

1994; Fujiwara et al. 1999). This ligament is highly fibrocartilaginous, both at its classic entheses on the lateral masses of the atlas and at its functional enthesis where it presses against the dens. In both regions, it immunolabels for type II collagen, aggrecan and link protein (Milz et al. 1999*b*). The alar ligaments too are highly fibrocartilaginous at their entheses (M. Benjamin, unpublished observations): hence the smooth facets for the ligaments at the apex of the dens.

Finally, we would comment that although some spinal lesions such as diffuse vertebral osteitis have traditionally *not* been viewed in relationship to enthesitis, it is known that enthesitis is associated with diffuse inflammatory changes in the bone, and thus most of the pathological changes in the spine could fit under the umbrella of enthesitis.

CONCLUSIONS

Spondyloarthropathies, and in particular ankylosing spondylitis and reactive arthritis, are strongly associated with HLA-B27. It has been suggested that a fibrocartilage-derived 'arthritogenic peptide' that binds to HLA-B27 triggers disease (Poole, 1998). What confuses the issue of course, is that sites of shear, compressive stressing and relative hypoxia, are also sites where fibrocartilage forms. It may be the propensity for microtrauma at these sites, and not fibrocartilage formation per se that is important in disease (McGonagle & Emery, 2000). The common factors at the anatomical sites of disease that we have discussed above have been overlooked, but we feel that these could be of immense importance in the immune activation. The immune response is not focused in a haphazard way in the bone rather it follows the lines of stressing in the bone (see fig. 2 in McGonagle & Emery, 2000). One possibility that needs exploration is that the microtrauma at disease sites interacts with bacteria or their products to trigger inflammation, and that this is amplified in subjects carrying an appropriate HLA gene, especially HLA-B27 (McGonagle & Emery, 2000). This has implications for defining putative autoantigens, as many cell types including fibroblasts, chondrocytes, osteocytes and immune cells in the bone marrow are common at diseased sites. Clearly, microbes play an important role in disease in addition to the biomechanical factors already mentioned. Support for an important role for bacteria comes from 2 experimental models of SpA with animals reared in germ-free conditions failing to develop disease (Taurog, 1994; Rehakova et al. 2000). The precise means by which biomechanical and microbial factors interact remains unclear, but synergy between both in immune activation has been considered (McGonagle & Emery, 2000).

Microtrauma is likely to be greatest where mechanical stressing is highest and we think it no coincidence therefore, that clinically recognised enthesopathy is more common in the lower than the upper limbs and most typical of the plantar fascia and Achilles tendon. Both have large entheses, vulnerable to high levels of stress. In animal models too (including the HLA-B27 transgenic rat model and mice with ankylosing enthesopathy, ANKENT), there is generally more disease in weight-bearing joints in the limbs—usually the ankle joint (Hammer, 1990). In the absence of recognised antigenic differences between these sites, then anatomical considerations are likely to be paramount in disease localisation. Furthermore, anatomical and biomechanical factors likely underscore the propensity for experimental arthritis in some animal models but not others and we feel that this is a potentially valuable avenue to explore disease susceptibility in man and in experimental models.

Thus we propose that anatomical factors are likely to play a pivotal role in disease localisation in SpA. Most of the sites of disease distribution including enthesitis, dactylitis, tenosynovitis, sacroilitis and osteitis, share common anatomical, biomechanical and even pathological features. A key anatomical clue is the widespread distribution of fibrocartilage, for this tissue is an adaptation to compression and/or shear. Of course the extraskeletal structures involved in SpA, namely the aortic root, the ciliary body in the eye, the lung apex and skin extensor surfaces (psoriasis) are also subject to considerable biomechanical stressing and microtrauma. The unifying anatomical basis for SpA proposed has implications for elucidating disease pathogenesis.

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